PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2002.745 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50829	International filing date *(day/month/year)* 13.11.2003	Priority date *(day/month/year)* 20.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/36		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.02.2004	07.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Borst, M Telephone No. +49 89 2399-8648

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50829

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-14 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-10
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	3-5,9,10
	No:	Claims	1,2,6-8
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO-A-9847517 (AKZO NOBEL N.V.) 29 October 1998 (1998-10-29)
D2: WO 00/23460 A (KIRCHHOLTES PETER HUUB GERARD ;SAS GERARD ARNOUD JOZEF MARIA (NL);) 27 April 2000 (2000-04-27)
D3: EP-A-0 927 556 (AKZO NOBEL NV) 7 July 1999 (1999-07-07)
D4: US 2002/044970 A1 (TAKEUCHI TOSHIO) 18 April 2002 (2002-04-18)

1. **Novelty (Article 33(2) PCT)**

The subject-matter of present claim 1 is not new in the light of D1.

D1 (claim 1) discloses pharmaceutical dosage units comprising 0.1 to 10% by weight of tibolone. According to D1 (page 5, line 14-16) the dosage unit can take the form of tablet provided with a film coat. Thus, the subject-matter of claim 1 on file can be arrived at after one selection only.

Lack of novelty occurs when the subject-matter on file can be derived directly and unambiguously from the prior art document. This is the case for D1, from the disclosure of which a film-coated tablet comprising 0.1 to 10% by weight of tibolone can be directly and unambiguously derived. It is not necessary for being pertinent to novelty that the the relevant disclosure is in the form of working examples or already marketed products.

Moreover, the term "stabilized" as used in claim 1 is a relative term and cannot be used for establishing novelty as long as the claim fails to define a reference point or the structural features providing the stabilisation. In fact the particular definition given to the term "coating" (cf. page 3, line 8-10) is not part of the claims. Once this is the case, it appears that a tablet comprising an amount of from 0.1 to 10% by weight tibolone and provided with a coating which achieves a stabilizing effect with respect to the formation of OM38 upon storage of a coated tablet as compared to an uncoated tablet cannot be derived from D1. D1 only in a general way discloses coated tablets. As is apparent from the experimental data on file (table 7) not any coating provides the stabilizing effect.

2. **Inventive step (Article 33(3) PCT)**

The subject-matter of claims 1-10 does not to involve an inventive step, since the

problem posed is not solved for whole range of the claim.
The problem to be solved according to the present application (page1, line 31-36) is to reduce degradation of tibolone in dosage forms. By comparison to uncoated tablet cores containing tibolone the applicant has shown (cf. examples) that said problem can be solved by the the provision of the following film coatings:
HPMC coat
HPMC coat + sucrose subcoat + sucrose topcoat
HPMC coat + sucrose topcoat
sucrose coat
PVA coat
Eudragit RL 30 D
For the claims on file the results of these experiments have been generalised to *any* kind of tablet core and to *any* kind of coating applied. However, it has been stated in the application (cf. page 3, line 35ff and example 5) that not all film coatings give the desired stabilizing effect on tibolone tablets. Moreover, it has been shown that the above problem is not solved by the the provision of the following film coatings:
Eudragit E PO
Eudragit L 100
Eudragit NE 30 D
Thus, the alleged effect of stabilising tibolone is not provided by all variants covered by the claims. The technical problem not being solved over the whole scope of the claims, inventive step cannot be acknowledged.
Due to the relative character of the term "stabilized" the claims are not restricted to those embodiments which actually provide a stabilisation in comparison to uncoated tablets. As already pointed out the particular definition given to the term "coating" (cf. page 3, line 8-10) is not part of the claims.
In view of 6 coatings that work versus 3 coatings that do not work, incorporating said definition into the claims and, thereby, restricting the claims to those coatings that "achieve a stabilizing effect with respect to the formation of OM38 upon storage of a coated tablet as compared to an uncoated tablet", would amount to claiming the underlying problem (Article 6 PCT). Therefore, for establishing inventive step, either further experimental data showing that the failure experienced with Eudragit E PO, Eudragit L 100, Eudragit NE 30 D is only exceptional, or restriction to those embodiments that actually work (page 4, line 22-24; claims 3-5, 9, 10) would be required.

This being the case, the requirements of inventive step appear to be met:
D1 (page 1, line 26 - page 2, line 14) and D2 (page 2, line 1-6; page 3, line 9-15) both deal with the degradation of tibolone. According to D1 said drawback can be overcome by increasing the amount of starch in the carrier. D2 tends to achieve the same result by aging tibolone crystals in water for at least 24 hours. The objective technical problem to be solved in the light of the closest prior art D1 or D2 is to provide an alternative solution for minimising the degradation of tibolone in dosage forms, such as tablets. None of the prior art documents available suggests a tablet coating for solving said problem. D3 ([0004]) proposes to apply a coating, however not for the purpose of reducing degradation of the steroids, but for the purpose of inhibiting migration of the steroids from the tablet core.